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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,005	09/11/2000	Erich Wanker	V0179/7001	1379

7590 10/01/2002

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EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/01/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,005	WANKER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 6/17/02 in Paper No. 12 is acknowledged and has been entered. Claims 1, 5-6, 8-13, 15-21 and 23-25 have been amended. Currently, claims 1-25 remain pending and are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "contacting said filter with material of a sample suspected to comprise said fibrils or aggregates" because it is unclear what is encompassed by the term "material" as used in the claim and how it relates to the "detergent" or "urea" in the preamble.

Claim 1 remains indefinite because it implies that the sample is exposed to "urea" or "detergent" for treatment, in order to detect presence of urea- or detergent- insoluble amyloid-like fibrils or protein aggregates, but fails to distinctly define it as such. It appears that the sample should be treated or caused to be solubilized by urea or detergent, to determine insolubility of proteins by such agents.

Claim 1 is indefinite because it recites, "contacting the filter with a sample ..." in step a), but fails to recite how the fibrils or aggregates are caused to be "retained" in the filter for detection excluding the detergent- or urea- soluble portion of the protein in the sample. Claim 1 fails to define that the filter functions to filter and retain detergent- or urea-insoluble fibrils or aggregates so that the soluble portion of the sample can be separated; thus, filtered. Alternatively, the mere recitation of "contacting the sample to a filter" fails to define that a "filtration function" is necessarily performed.

Claim 6 is indefinite in using inconsistent terminology by using the term "material" to make reference to different elements in a given set of claims, i.e. claim 1 recites undefined "material" of a sample and claim 6 recites a "material" to make reference to the filter.

Claim 8 is vague and indefinite in reciting, "material of the sample" because it is unclear what is encompassed by the term "material" as used in the claim.

Claim 9 is vague and indefinite in reciting, "material of the sample" because it is unclear what is encompassed by the term "material" as used in the claim.

Claim 9 is confusing in relation to claim 1 in reciting, "material is simultaneously with ... step a), sucked through said filter" because claim 1 fails to define that the sample is soluble or solubilized (see comments for claim 1).

Claim 10 is vague and indefinite because it is unclear how detection in step b) is effected by antibody, peptide, enzyme, or chemical agent in the absence of a label or a signal producing system.

Claim 12 is vague and indefinite in reciting, "material of the sample" because it is unclear what is encompassed by the term "material" as used in the claim. Perhaps, Applicant intends "wherein said sample". See also claim 18.

Claim 13, step a') is indefinite and confusing because it is unclear how the "fusion protein" and its incubation with a suspected inhibitor of fibril or aggregate formation or a compound that induces cleavage, relate structurally and functionally to the "material of a sample" recited in claim 1, step a), and urea- or detergent- insolubility in the preamble of claim 1.

Claim 21 is vague and indefinite reciting, "An inhibitor of ... identified by the method of claim 14 because any one of claims 1-3, 7, 13, and 14 do not appear to recite method claims to identify this "inhibitor".

Claim 24 is indefinite and confusing in reciting, "the fusion protein of any one of the preceding claims because claims 1-12 do not appear to recite or define a "fusion protein". Thus, claim 24 lacks clear antecedent basis in such a recitation.

Claim 24 is objected to under 37 CFR 1.75(c) as being an improper multiply dependent claim because a number of the preceeding claims are multiply dependent, so claim 24 cannot depend from more than one of them. See MPEP § 608.01(n).

Claim 25 is vague and indefinite in reciting, "The diagnostic composition of claim 24 (comprising the fusion protein) further comprising "the filter" because it is unclear how the "filter" is part of the "fusion protein" as a diagnostic composition in claim 24.

Claim 25 is indefinite and confusing in reciting, "the compound that induces cleavage of any one of the preceding claims". Please clarify. Also, claims 1-12 do not

appear to recite, "inducing a cleavage". Thus, claim 25 lacks clear antecedent basis in such a recitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3, 5-12, and 18-19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tateishi et al (Membrane, 1993) for reason of record.

Tateishi et al. teach a method of detecting and removing detergent insoluble amyloid-like fibrils or protein aggregates (prion protein or PrPCJD) from the brain sample of mice with spongiform encephalopathy using a filter (virus removal membrane) which is cuprammonium regenerated cellulose hollow fiber (see Abstract and page 358, column 1). Filters for use in protein aggregate removal are commercially known with different mean pore sizes ranging from 35 nm to 75 nm (see page 358, column 2). Filtration is carried out under constant transmembrane pressure of 180 mmHg at 20 C. The existence of detergent insoluble amyloid-like fibrils or protein aggregates indicative of the neurodegenerative disease (agent infectivity) is confirmed by treatment with a detergent (surfactant), i.e. Sarkosyl (see page 361, column 2). The presence of PrPCJD protein in the filter is detected immunohistchemically using a chemical reagent (see page 359, column 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 4 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Trottier (Nature, 1995) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) for reason of record.

Tateishi et al. teach a method of detecting and removing detergent insoluble amyloid-like fibrils or protein aggregates (prion protein or PrPCJD) from the brain sample of mice with spongiform encephalopathy using a filter (virus removal membrane) which is cuprammonium regenerated cellulose hollow fiber (see Abstract and page 358, column 1). Filters for use in protein aggregate removal are commercially known with

different mean pore sizes ranging from 35 nm to 75 nm (see page 358, column 2). Filtration is carried out under constant transmembrane pressure of 180 mmHg at 20 C. The existence of detergent insoluble amyloid-like fibrils or protein aggregates indicative of the neurodegenerative disease (agent infectivity) is confirmed by treatment with a detergent (surfactant), i.e. Sarkosyl (see page 361, column 2). The presence of PrPCJD protein in the filter is detected immunohistchemically using a chemical reagent (see page 359, column 2).

Tateishi et al. differ from the instant invention in failing to teach that the neurodegenerative diseases are associated with a polyglutamine expansion of proteins.

Trottler et al. teach neurodegenerative diseases such as in Huntington's disease which are associated with polyglutamine expansion of specific proteins. Trottler et al. teach that pathological threshold for these proteins, is 37-40 glutamine expansion whereas the corresponding normal proteins contain polymorphic repeats of up to 35 glutamines (see Abstract). Trottler et al. characterize monoclonal antibodies that selectively recognize polyglutamine expansion in proteins and use them to detect presence of polyglutamine stretch on Western Blot (see page 403, column 1).

Stott et al. teach that some transcription factors and proteins contain polyglutamine repeats and their abnormal expansion is linked to neurodegenerative diseases. Stott et al. teach that polyglutamine forms B-strands which are held together by hydrogen bonds between their amide groups, thus, forming polar zippers. Multiplicity of hydrogen bonds between extended strands of glutamine repeats in an oligomer increases stability of these proteins (see page 6509). Stott et al. teach that pathological

effects and abberant transcriptional activity arise when expanded glutamine repeats cause proteins to acquire excessively high affinities for each other or for complementary regulatory proteins with glutamine repeats (see page 6512).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect proteins having polyglutamine expansion as taught by Trottler and Stott, using the method and device of Tateishi which utilizes cuprammonium regenerated cellulose hollow fiber in acquiring and detecting insoluble amyloid-like fibrils and protein aggregates because Stott specifically taught that proteins with polyglutamine expansion have excessively high affinities with each other; thus, providing stability and insolubility to certain protein aggregates and Tateishi specifically taught application of his method for capture and detection of such insoluble protein aggregate forms.

5. Claims 13-14, 16, and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) for reason of record.

Tateishi et al. has been discussed supra. Tateishi et al. differ from the instant invention in failing to teach a fusion protein as described in claim 13.

Smith discloses a fusion protein comprising an amyloidogenic polypeptide (foreign protein or peptide) that aggregates into amyloid-like fibrils or protein aggregates fused with a polypeptide (glutathione-S- transferase) that enhances solubility or prevents aggregation. An enzymatically cleavable link is preferably provided in the

fusion protein between the glutathione-S-transferase and the insoluble foreign protein (see Abstract and columns 3 and 5). Smith teaches that insoluble or partially soluble fusion proteins can be purified by affinity chromatography if they are solubilized in a solubilizing agent which does not disrupt binding to glutathione agarose such as Triton X-100 or dithiothreitol. Insolubility has been associated with increased protein stability (see column 4).

Stott et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect the presence of detergent or urea insoluble amyloid-like fibrils such as taught by Tateishi in a partially or wholly insoluble fusion protein such as taught by Smith because Tateishi specifically taught application of his method for capture and detection of insoluble protein aggregate forms including those manifested in neurodegenerative diseases in the teaching of Stott and the fusion protein specifically described and characterized by Smith as being in insoluble or partially soluble form.

6. Claims 15 and 21-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) as applied to claims 13-14, 16, and 20 above, and further in view of Vitck et al. (US 5,935,927) for reason of record.

Tateishi et al., Smith, and Stott et al. have been discussed supra. Tateishi et al., Smith, and Stott et al. differ from the instant invention in failing teach an inhibitor of amyloid-like fibril or protein aggregate formation.

Vitck et al. disclose that advanced glycosylation end-products (AGE)- amyloid polypeptides, i.e. AGE-β amyloid peptide (βAP) facilitate aggregation of amyloid fibrils in neurodegenerative diseases such as Alzeimer's disease (see column 5, lines 42-64, columns 9 and 11). Further, Vitck et al. disclose treatment of neurodegenerative disease using pharmaceutical compositions comprising inhibitors that prevent formation or cross-linking of AGE proteins resulting to amyloidosis and formation of amyloid fibrils (see columns 13-15).

One of ordinary skill in the art at the time of the instant invention would have been motivated to inhibit formation of amyloid fibrils in neurodegenerative diseases such as in the teaching of Tateishi, Smith, and Stott using inhibitors in the form of pharmaceutical compositions such as taught by Vitck because Vitck specifically taught that such inhibitors prevent facilitated aggregation of amyloid fibrils in neurodegenerative diseases such as set forth in the claimed invention.

Response to Arguments

7. Applicant's arguments filed 6/25/02 have been fully considered but they are not persuasive.

A) Applicant argues that claim 9 in relation to claim 1 is clear because it is apparent to one skilled in the art that the detergent- or urea- soluble material of the sample can be sucked through the filter upon simultaneous contact with the filter.

In response, claim 1 fails to distinctly define that the sample is soluble or solubilized, and can be allowed to be filtered or sucked; only that the "filter is contacted with material of a sample (see comments for claim 1). Specifically, the preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

B) Applicant argues that the claims are not anticipated by Tateishi et al. nor are they suggested by Tateishi et al. in view of combinations of Trottier et al., Stott et al., Smith, and Vitck et al. because in the presence of the detergent Sarkosyl, Tateishi recites that the aggregates were separated into small pieces; thus, were solubilized and diluted into smaller pieces and no longer contained in the filter membrane but in the corresponding filtrate. Applicant argues that the "aggregates" described in Tateishi et al. were in fact soluble by detergent and that Tateishi is not detecting the presence of insoluble fibrils.

In response, Tateishi et al., indeed, teach and suggest the claimed invention as recited. Specifically, Tateishi et al. estimates the aggregation state of CJD infectious

agents after exposure with Sarkosyl detergent using double filtration method by using 2 filter membranes with differing pore size, i.e. 60 nm and 40 nm, which can retain and remove from the filtrate, 60 nm and 40 nm sized insoluble particles, respectively. The treatment by Sarkosyl reagent caused some portions of the protein to solubilize; thus dispersing particles into less than 40 nm sizes which cannot be retained by the 40 nm pore size; however, the existence of insoluble protein aggregates after treatment by Sarkosyl are found as follows: 1) retained in the 60 nm filter membrane (>60 nm aggregates), 2) retained in the 40 nm filter membrane (>40 nm aggregates), and filtered through the filter membranes (<40 nm aggregates) and detected therefrom. According to Tateishi et al., the content of larger "insoluble" particles that are retained in the filter membrane is 99.99% of the total amount of the infectious agent. The smaller insoluble particles <40 that permeated through the 40 nm pore size filter, increased infectivity of the Sarkosyl treated filtrate sample in comparison to the untreated or unsolubilized filtrate sample; thus confirming the presence of smaller sized Sarkosyl insoluble protein aggregates in the filtrate.

Alternatively, claim 1 only recites that the filter is contacted to a sample suspected to comprise fibrils or aggregates, which are recited in the preamble as urea- or detergent- insoluble, and detecting whether said fibrils or aggregates are retained on the filter. There does not appear to be a filtration step in the method steps, there is no requirement of a pore size to the filter, or particle size for the fibrils or protein aggregates, there is no requirement that the protein fibrils or aggregates are retained on the filter for detection (only requires detecting as to whether the fibrils or aggregates are

retained on the filter), there is no standard for ascertaining the requisite degree or metes and bounds of what is defined as "insoluble" versus "soluble"; and since solubility is defined as dissolution of solids into solvent, any existence of aggregates, albeit retained on the filter or filtered through a filter membrane depending on pore size of the filter, renders the protein fibril or aggregate, insoluble. Therefore, Tateishi et al. is said to both anticipate and further suggest the claimed invention.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

8. For reason aforementioned, no claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
September 30, 2002

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641